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LETTER TO THE EDITOR

WILEY

Effectiveness of traditional Vietnamese medicine Kovir capsule in adults with mild COVID-19: A propensity score-matched study

Dear Editor-in-Chief,

As of September 5, 2022, over 600 million people have been confirmed with coronavirus disease 2019 (COVID-19) worldwide; nearly 6.5 million deaths were reported (World Health Organization, 2022c). More than 12 billion vaccine doses have been administered; however, since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly evolved and created new variants, the duration of protection and efficacy of current vaccines are uncertain. Therefore, an urgent need for effective treatments for COVID-19 still remains. Based on the formula of *Ren Shen Bai Du San*, a famous traditional remedy, a hard-capsule Vietnamese herbal medicine named "Kovir" has been developed to support the treatment for patients with COVID-19 in Vietnam. Previously, a phase-2 trial showed that Kovir capsule (TD0069) was safe and had potential effects on symptom resolution and prevention of progression to severe diseases for patients with mild COVID-19 (Loc et al., 2022).

To better prove these findings, we conducted a non-randomized study in adults (aged ≥18 years) with mild COVID-19 (confirmed via a positive reverse transcription polymerase chain reaction [RT-PCR] for SARS-CoV-2) admitted to Temporary Hospital for COVID-19 No. 3 (Ho Chi Minh city, Vietnam) from July to September 2021. A total of 1,000 patients were consecutively recruited to the study; the first 700 patients received Kovir capsule combined with standard treatment (Kovir group) and the subsequent 300 patients received standard treatment only (control group). Standard treatment included antipyretics, adequate nutrition, and rehydration according to the World Health Organization (WHO) guidelines (World Health Organization, 2022a). In the Kovir group, oral Kovir hard capsule (three capsules three times a day [nine capsules daily in total]) was added. As described elsewhere (Loc et al., 2022), there are 12 herbal ingredients in a Kovir capsule; all harmonize to facilitate the reconcilement and recovery of the body.

TABLE 1 Baseline characteristics and clinical outcomes

	Before matching			After matching		
	Kovir ($N = 700$)	Control ($N = 300$)	*p* value	Kovir ($N = 265$)	Control ($N = 265$)	*p* value
Baseline characteristics						
Sex male	340 (48.6)	146 (48.7)	1	126 (47.5)	126 (47.5)	1
Age, years	37.5 ± 12.0	40.7 ± 13.1	<.001	41.1 ± 12.7	40.4 ± 13.1	.531
Nutritional status			.518			.753
Underweight (BMI < 18.5)	30 (4.3)	13 (4.3)		13 (4.9)	12 (4.5)	
Normal weight (18.5 ≤ BMI < 25)	634 (90.6)	278 (92.7)		240 (90.6)	244 (92.1)	
Overweight (25 ≤ BMI ≤ 30)	33 (4.7)	9 (3.0)		12 (4.5)	9 (3.4)	
Obesity (BMI > 30)	3 (0.4)	0 (0.0)		0 (0.0)	0 (0.0)	
Hypertension	4 (0.6)	4 (1.3)	.250	3 (1.1)	3 (1.1)	1
Diabetes	0 (0.0)	1 (0.3)	.300	0 (0.0)	1 (0.4)	1
Heart failure	0 (0.0)	1 (0.3)	.300	0 (0.0)	1 (0.4)	1
Overall symptom score	7.0 ± 4.5	7.9 ± 4.0	<.001	8.1 ± 5.2	7.4 ± 3.5	.694
Clinical outcomes						
Progression to severe disease	0 (0.0)	18 (6.0)	<.001	0 (0.0)	17 (6.4)	<.001
Hospital length of stay, days	11.7 ± 2.6	11.9 ± 2.2	.308	11.8 ± 2.7	12.0 ± 2.3	.309

Note: Summary statistics are *n* (%) or mean ± standard deviation.
Abbreviation: BMI, body mass index.

The investigators examined the patients at enrollment (day 0), day 1, once every two days, and at discharge to assess symptom severity and safety. There were 18 symptoms of interest: nasal secretion, nasal congestion, sneeze, sore throat, hoarseness, cough, chest pain, headache, loss of smell, loss of taste, dizziness, fatigue, muscle pain, fever, chill, sweating, feeling sleepy, and other symptom. Each symptom was ranked on a scale of 0 (absence of the corresponding symptom), one (mild), two (moderate), and three (severe). The overall symptom score was the total score of all 18 symptoms. The investigators also assessed clinical adverse events and daily vital signs (body temperature, heart rate, blood pressure, and saturation of peripheral oxygen [SpO_2]) to evaluate the safety and progression to severe disease. Patients were discharged when having no fever for at least two days plus a negative RT-PCR result. The outcomes were time to symptom resolution, daily symptom severity score, and progression to severe or critical COVID-19 which was defined based on the WHO guidelines (World Health Organization, 2022a, 2022b).

Propensity score-matched (PSM) analysis was used to adjust for imbalances in baseline characteristics between groups including sex, age, nutritional status based on body mass index (BMI), comorbidities, and symptom score at enrollment. Among 1,000 participants included in the study, the PSM strategy resulted in 530 patients (265 in each group). Baseline characteristics of the patients were more balanced between the two groups after matching (Table 1).

A total of 18 patients progressed to severe disease, and all were in the control group. After matching, 17 patients (6.4%) in the control group and none in the Kovir group had disease progression, leading to a significant difference between groups regarding this outcome. Hospital length of stay was similar between the two groups (mean was approximately 12 days) (Table 1).

Daily symptom severity score differed between groups (Figure 1A,B). After matching, symptom scores decreased more rapidly in the Kovir group than in the control group from day 5 onwards. The Kovir group significantly reduced time to symptom resolution compared to the control group in both the analyses

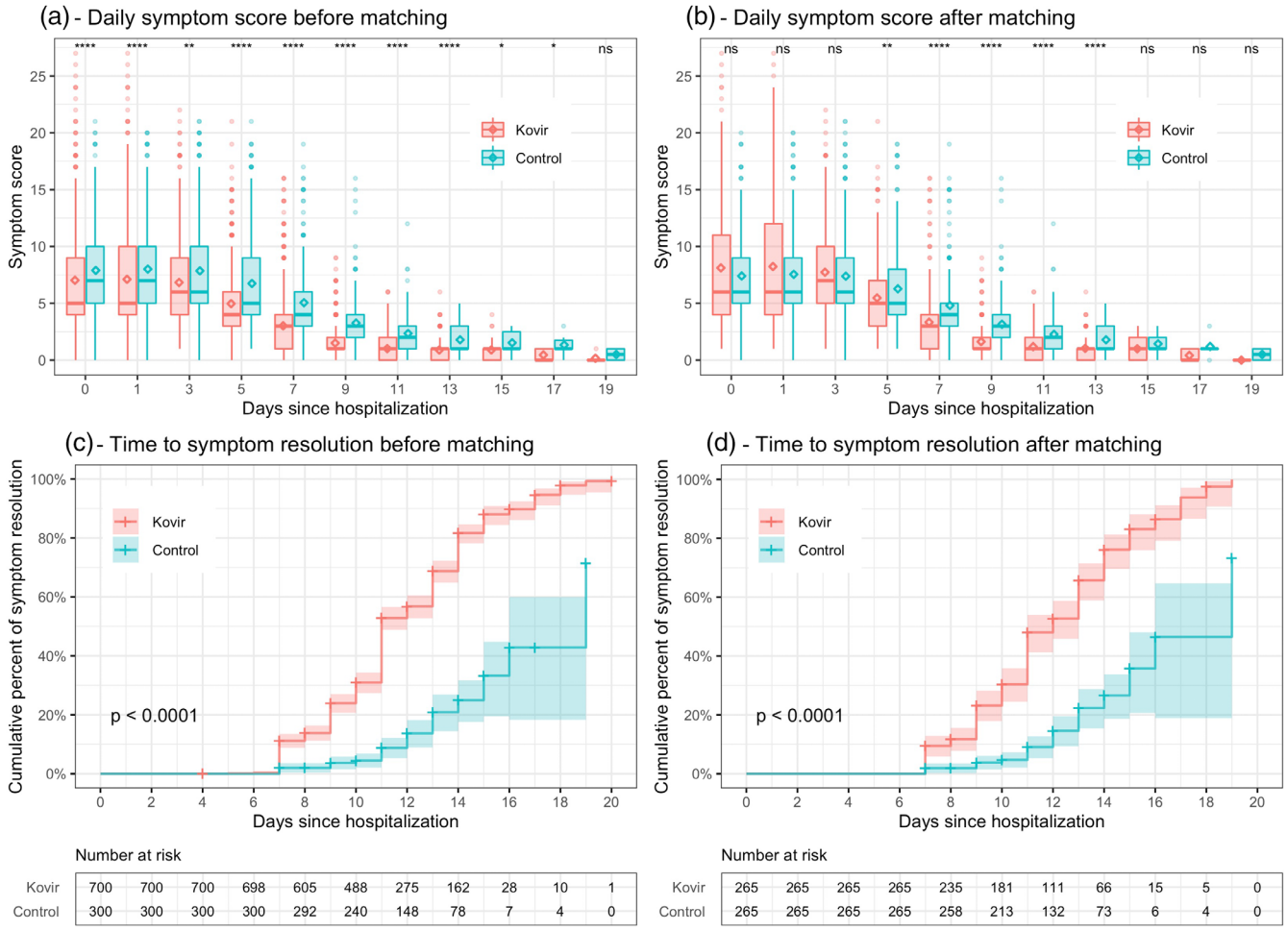

FIGURE 1 Daily symptom score and time to symptom resolution by treatment groups. In (a) and (b), the line inside each box is the median, the upper and lower margins of each box are the 25th and 75th percentiles, and the diamond inside each box is the mean of symptom score. Mann–Whitney-*U* test is used to compare symptom scores between the two groups and symbols indicating statistical significance are presented in the top of each plot: **** < .0001 < *** < .001 < ** < .01 < * < .05 < ns. ns, not significant. In (c) and (d), lines are the Kaplan–Meier estimates and colored regions are 95% confidence intervals

before and after matching (Figure 1C,D). Median time to resolution of all symptoms were 11 and 19 days before matching, and 12 and 19 days after matching, in the Kovir and control groups, respectively.

Many herbal and traditional medicines have also been investigated for the treatment of COVID-19 in some countries with well-known traditional medicine such as China, India, and Iran (Chen et al., 2022; Devpura et al., 2021; Jiang et al., 2021; Karimi et al., 2021; Natarajan et al., 2021; Srivastava et al., 2021; Valizadeh et al., 2020; Varnasseri et al., 2022; Xia et al., 2021; Xiao et al., 2020; Xu et al., 2021; Zhang, Lv, et al., 2021; Zhou et al., 2021). A highlighted feature of herbal and traditional medicines is symptom relief that can reduce time to symptom resolution and prevent the progression to severe disease. Some studies also show the ability of viral clearance of some herbal medicines (Devpura et al., 2021; Natarajan et al., 2021; Srivastava et al., 2021; Xu et al., 2021). However, since COVID-19 pathogenesis contains a complex interplay between the virus and host immune response and there is still no evidence that the viral load is associated with disease severity (Abdulrahman, Mallah, & Alqahtani, 2021; Shenoy, 2021; Zhang, Xiang, et al., 2021), an effective drug can improve clinical outcomes without an effect of viral clearance. A limitation of our study is that we used subjective assessments to evaluate the symptom score and the tool had not been validated in advance due to the severe outbreak situation. We therefore also focused on another objective outcome which was the prevention to disease progression. Although a few patients experienced disease progression to severe/critical COVID-19, the study still showed the effectiveness of Kovir regarding this outcome. This could be due to a possible property of Kovir, which is healing and restoring balance of the body.

Following the phase-2 trial on Kovir (Loc et al., 2022), this study confirms the clinical effectiveness of Kovir for mild COVID-19 patients. Kovir facilitates relieving symptoms, shortens time to symptom resolution, and prevents disease progression to severe COVID-19. No new safety concern was observed in this study. We encourage the use of this herbal medicine in combination with standard treatment for COVID-19 patients.

This study was conducted within the same outbreak with the previous phase-2 trial on Kovir (Loc et al., 2022), in which the Delta variant dominated in our country. Currently, the Omicron variant is the most prevalent in the world. Whether Kovir capsule is efficacious in different variants of SARS-CoV-2 is questioned. A phase-3 trial on Kovir has been conducting in the Omicron era and it will answer this question.

AUTHOR CONTRIBUTIONS

Huynh Nguyen Loc: Conceptualization, Methodology, Writing–Review & Editing; **Truong Thi Ngoc Lan**: Conceptualization, Methodology, Writing–Review & Editing; **Dinh Thi Lan Huong**: Conceptualization, Methodology, Data Curation, Project administration, Writing–Review & Editing; **Nguyen Thanh Tuyen**: Methodology, Data Curation, Writing–Review & Editing; **Tran Minh Quang**: Methodology, Data Curation, Writing–Review & Editing; **Ly Minh Dao**: Methodology, Data Curation, Writing–Review & Editing; **Nguyen Lam Vuong**: Methodology, Formal analysis, Writing–Original Draft.

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CONFLICT OF INTEREST

All authors confirm that they have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, NLV, upon reasonable request.

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